

**REMARKS**

Claims 1-23 were pending in the application, as filed. Claims 2-4 are cancelled above and new claim 24 is added. Claims 1, and 5-24 therefore, are pending with claims 20-23 withdrawn from consideration as being drawn to a non-elected invention. Reconsideration in view of the above amendments and following remarks is respectfully requested.

***Specification***

The specification is objected to because: 1) the specification contains a reference to claim 1 on page 7; 2) the specification refers to Figures 3a and 3b rather than Figures 3 and 4; and 3) the specification does not contain section headings.

The specification is amended above to delete reference to the claims and to bring the description of the drawings into agreement with the drawings, which were amended on May 23, 2007 in response to an objection to the drawings contained in a Notification of Missing Requirements. At that time, original Figure 3a was renumbered Figure 3 and original Figure 3b was renumbered Figure 4. No new matter was added by the amendment.

Lastly, the specification is further amended to include section identifiers.

***Rejections Under 35 U.S.C. §112, second paragraph and §101***

The claims are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Additionally, claims 13-19 are rejected under 35 U.S.C. §101 because the claimed recitation of a use without setting forth any steps involved in the process results in an improper process claim.

The claims are amended above to remove terms which the Office Action alleges renders the claims vague and definite. Additionally, claim 1 as amended, recites positive method steps

and claims 13-19, which are dependent from claim 1 include those recitation steps. Lastly, the claims are amended to correct any lack of antecedent bases.

In view of the amendments, the rejections under 35 U.S.C. §112, second paragraph and §101 are overcome and reconsideration and withdrawal of the rejections are respectfully requested.

***Rejection Under 35 U.S.C. §112, first paragraph***

The claims are rejected under 35 U.S.C. §112, first paragraph as lacking enablement for the full scope of the claims. According to the Office Action, the specification is enabling for a method for detecting C-terminal fragments of preproendothelin-1 (SEQ ID NO: 1) in a sample selected from the group consisting of whole blood, plasma or serum, wherein the sample is collected from a human patient suffering from cardiovascular disease, systemic inflammatory response syndrome, and sepsis by contacting the sample with antibodies which specifically bind within amino acids 168-181, 184-203 and 200-212 of preproendothelin-1. However, the Office Action states that:

“The specification fails to teach any and all antibodies [that] bind to any and all sequence combinations of amino acids 93-212 of preproendothelin-1....Thus, such is not seen as sufficient to support the breadth of the claims one skilled in the art cannot practice the claimed invention without undue experimentation, because in order to have a high level of predictability, one skilled in the art would have to know that all antibodies to amino acids 93-212 of preproendothelin-1 would bind to any position within amino acids 93-212 and that these antibodies would detect the C-terminal fragments of preproendothelin-1 in samples from patients suffering from cardiovascular diseases, inflammations, sepsis, and cancer.”

The claims as amended above recite positive method steps for determining the formation of endothelin in certain patient populations by measuring the level of a C-terminal fragment of preproendothelin-1, which is generated in the formation of endothelin-1 and big endothelin-1, using first and second antibodies which specifically bind to first and second epitopes within

amino acids 168-212 of preproendothelin-1. Support for the amendment can be found throughout the specification, and for example in original claim 4.

Endothelin is a 21 amino acid vasoconstrictor that has been implicated in a number of diseases, including cardiovascular disease (specification page 3, lines 27-33). Its residence time in the circulation, however, is very short, making it an unreliable measure of how much endothelin is actually being produced.

Applicants set out to indirectly determine the quantity of endothelin formed by measuring the amount of an inactive fragment from preproendothelin, the precursor molecule from which endothelin-1 and big endothelin-1 are formed. Applicants identified a specific region of preproendothelin, that is, amino acids 168-212, and generated antibodies against peptides from this region. Applicants then showed that they were able to measure in individuals known to have cardiovascular disease, SIRS, sepsis, severe sepsis and septic shock, the levels of the preproendothelin fragment remaining after endothelin has been cleaved. Because of the stoichiometric relationship between endothelin and its precursor, the amount of preproendothelin fragment detected in the patient sample represents the amount of endothelin formed from the prohormone.

### **Enablement**

An application satisfies the enablement requirement if one skilled in the art, after reading the disclosure, could practice the invention claimed without undue experimentation *In re Wands*, 858 F.2d 731. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation “must not be unduly extensive.” *Chiron Corporation v. Genentech, Inc.*, 363 F.3d 1247. Only after it has been determined that additional experimentation is required, does an analysis under the Wands factors, of whether that experimentation is undue, become applicable.

Furthermore, a patent disclosure need not enable information within the knowledge of an ordinary artisan. In the instant case, the claimed method is a dual antibody assay, where the antibodies are directed to a region of preproendothelin-1 which Applicants identified as a

clinically relevant surrogate marker. Dual antibody, or “sandwich” assays are well known in the art. Once the identity (amino acid structure) of the analyte to be measured is disclosed, one of skill in the art can readily produce antibodies that will specifically bind to that molecule, because the methodologies required for generating and screening antibodies are also well known to those of skill in the art.

“The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art: *Ansul Co. v. Uniroyal, Inc.* supra. The test is not merely quantitative, since *a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.* The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims.”

*Ex parte Forman*, 230 USPQ 546, 547-548 (B.P.A.I. 1986) emphasis added.

The key word is “undue,” not “experimentation.” In *Wands*, claims to antibodies that required a screening procedure to isolate the desired hybridoma cells from enormous numbers of other cells present in a reaction mixture were held to not require experimentation that was “undue.” *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The amount of effort required to make the antibodies was “not excessive.” Thus, in view of Applicants’ disclosure of the identity and structure of a surrogate marker for endothelin-1 and/or big endothelin-1, in this case amino acids 168-212 of preproendothelin-1, the general knowledge of one of skill in the art would, as a matter of routine, enable her to make and screen the appropriate antibodies for a dual antibody assay for the detection of amino acids 168-212 of preproendothelin-1.

Furthermore, the specification provides three working examples of antibodies that were made against the 168-212 region of preproendothelin-1 (see page 16, line 18 to page 17, lines 1-4), and two examples of dual antibody assays, using different combinations of the three antibodies. The enablement requirement is met if the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope

of the claim. *In re Fisher*, 427 F.2d 833, 839, 166 USPW 18, 24 (CCPA 1970). Furthermore, it has long been settled that, even in biotechnology, multiple examples are not essential to satisfy the enablement requirement. *In re Strahilevitz*, 668 F.2d 1229, 1232 212 USPQ 561, 563 (CCPA 1982) (working examples are not required to satisfy enablement for immunological method of removing haptens from blood of a mammal.)

Nonetheless, examples are provided in the specification, which demonstrate the detection of a molecular species comprising amino acids 168-212 of preproendothelin.

Applicants respectfully submit that no additional guidance is necessary and no undue experimentation is required for one of skill to practice the claimed method.

The Examiner is invited to contact Applicants' Attorney at the telephone number given below if any further questions arise in connection with this Application.

*Respectfully submitted,*



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